PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 509015 JBM	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. **PCT/NZ2004/000196**	International filing date *(day/month/year)* 23 August 2004	Priority date *(day/month/year)* 22 August 2003
International Patent Classification (IPC) or national classification and IPC **Int. Cl.** [7] C07F 9/54, A61K 33/42		
Applicant ANTIPODEAN BIOTECHNOLOGY LIMITED et al		

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 7 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *(sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or table related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).
4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	~~Box No. VII~~	~~Certain defects in the international application~~
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of the report
22 June 2005	25 November 2005
Name and mailing address of the IPEA/AU AUSTRALIAN PATENT OFFICE PO BOX 200, WODEN ACT 2606, AUSTRALIA E-mail address: pct@ipaustralia.gov.au Facsimile No. (02) 6285 3929	Authorized Officer **JAMIE TURNER** Telephone No. (02) 6283 2071

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NZ2004/000196

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:

☐ international search (under Rules 12.3 and 23.1 (b))

☐ publication of the international application (under Rule 12.4)

☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements** of the international application, this report is based on (*replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report*):

☒ the international application as originally filed/furnished

☐ the description:

pages as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☐ the claims:

pages as originally filed/furnished
pages* as amended (together with any statement) under Article 19
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☐ the drawings:

pages as originally filed/furnished
pages* received by this Authority on with the letter of
pages* received by this Authority on with the letter of

☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing.

3. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

☐ the description, pages
☐ the claims, Nos.
☐ the drawings, sheets/figs
☐ the sequence listing (*specify*):
☐ any table(s) related to the sequence listing (*specify*):

* *If item 4 applies, some or all of those sheets may be marked "superseded."*

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/NZ2004/000196

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos: 1-5, 11–15, 32–36, 53, 54, 60–62, 77, 78, 91-94, 108–110, 114–119 (all partially)

because:

☐ the said international application, or the said claims Nos.
relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos.
are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos.
are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claim Nos. 1–5, 11–15, 32–36, 53, 54, 60–62, 77, 78, 91–94, 108–110, 114–119 (all partially)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form
- ☐ has not been furnished
- ☐ does not comply with the standard

the computer readable form
- ☐ has not been furnished
- ☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details.

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims **12, 20–29, 32–52, 58–61, 65–74, 81–90, 96–105, 111–113. (some claims partially – see Box III)**	**YES**
	Claims **1–11, 13-19, 30, 31, 53-57, 62–64, 75–80, 91–95, 106–110, 114-119.**	**NO**
Inventive step (IS)	Claims **12, 20–29, 41–50, 58, 59, 65–74, 81–90, 96–105, 111–113. (some claims partially – see Box III)**	**YES**
	Claims **1–11, 13-19, 30–40, 51-57, 60–64, 75–80, 91–95, 106–110, 114-119.**	**NO**
Industrial applicability (IA)	Claims **1–119.**	**YES**
	Claims	**NO**

2. Citations and explanations (Rule 70.7)

The following documents, first cited in the International Search Report, are referred to as follows:

D1 - WO 2003/016323
D2 - KELSO, G. F., et. al. Annals of the New York Academy of Sciences 959:263-74.
D3 - JAUSLIN, M. L. el. al. The FASEB Journal 17(13):1972-4.
D4 - KELSO, G. F., et.al. The Journal of Biological Chemistry 276(7):4588-96.
D5 - US 6331532
D6 - SARETZKI, G., et. al. Aging Cell 2:141-3

Novelty (N) and Inventive Step (IS)

D1 discloses the preparation of the synthesis of certain triphenylphosphonium quinols and quinones falling within the scope of the compounds claimed in claims 1-10 and 53-57. The claimed compounds are not restricted to being used in any particular manner, and therefore claims 1-10 and 53-57 lack novelty and inventive step. The citation does not suggest that the compounds are manufactured into pharmaceutical compositions, or that they are used in any particular manner. The citation does not suggest that the method of manufacture would include the use of cyclodextrin. Therefore the claimed compositions, and methods of use and preparation are novel and inventive in view of D1.

D2 discloses that certain triphenylphosphonium quinols and quinones, falling within the scope of claims 1-10 and 53–57, prevent oxidative damage in the mitochondria. This is ascertained in part by administering the compositions of the compounds to mice. Therefore the compounds of claims 1-10 and 53-57 lack novelty and inventive step. It is acknowledged that the claims do specify that the 'anionic complement does not exhibit reactivity against the antioxidant moiety, the cationic moiety or the linking moiety', but it not apparent that any reactivity, or decrease in the concentration that may be observed over time, is necessarily a consequence of the anion. It is considered that the compounds used in D2 have a high level of stability, although it may not be as high as the mitoquinone-cyclodextrin complexes of the present application.

The pharmaceutical compositions of claims 11, 13-19, 62-64, 114 and 115 lack novelty and inventive step. D2 does not suggest that the compounds are complexed with cyclodextrin, and therefore it is suggested that the pharmaceutical compositions of claims 20-31 and 65-76, and the dosage units of claims 41-52, and the methods of treatment of claims 81-90 and 96-107, methods of synthesis of claims 111-113 may be novel and inventive.

(continued in Supplemental Box)

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

The invention is not clearly described. It appears that the invention relates to providing stable mitochondrially active antioxidants. The specification indicates that mitoquinone/mitoquinol compounds are not sufficiently stable as the bromide salt, implying that these are not satisfactory. (p. 3, line 17 – p. 4 line 2, p. 73 line 29 – p. 74 line 3, Table 2, Fig. 11). However, the description notes that preferred antioxidant compounds are those with a bromide salt (p. 34 line 9 – 11) and that examples of pharmaceutically acceptable anions include halogen ions, including bromide. (p. 35 line 19 – p. 36 line 2). The specification also prepares a bromide salt of mitoquinone. (Example 2, Fig. 2c) These teachings appear to be contradictory. The specification also discusses and prepares mesylate salts of mitoquinone, as well as complexes with cyclodextrin. It may be that only the cyclodextrin-mitoquinone complexes actually support an improved stability in order to overcome the problems identified in the prior art. It is apparent that even though the cyclodextrin-mitoquinone complexes actually demonstrate improved stability over the bromide salt, it is still not stable to the extent that it is perfectly stable. (see Table 4) It is quite unclear from the description as to the scope of the compounds envisaged as overcoming the problems of the prior art, and which are distinguished as being those compounds of the invention. It would be clearer if the specification clearly described in explicit terms the scope of the compounds of the invention.

Claims 1 – 5, 11 – 15, 32 – 36, 53 - 55, 60 – 62, 77, 78, 91 – 94, 108 - 110, 114 – 119 are not fully supported by the description. It is quite speculative to attempt to claim all possible compounds (and their uses) based on a desirable antioxidant activity when located in the mitochondria, or to specify the activity of the anion and that it is 'not a halogen ion'. It would be better to provide explicit details of the compounds (and their anions) that are within the scope of the claim, in terms of the support provided in the description. The only support provided for compounds having the alleged effects as claimed are those having mitoquinone type structures. Hence those claims which do not refer to compounds having a mitoquinone type structure, lack support.

It may be that claims 6 – 10, 16 – 19, 37 – 40, 56, 57, 63, 64, 72, 79, 80 and 95 are also not fully supported, because if the invention relates to providing a mitochondrially active antioxidant having improved stability over the bromide salt of mitoquinone/mitoquinol (p. 3 line 17 – p. 4 line 2, p. 73 line 29 – p. 74 line 3) then the only support actually provided is when mitoquinone is complexed with cyclodextrin. (see also first observation above).

Claims 111 and 112 purport to be to a method of preparing certain mitoquinone compounds, which involves the use of cyclodextrin. It is quite unclear how the use of cyclodextrin assists in bringing about preparation of these compounds.

Supplemental Box

In case **the space in any of the preceding boxes is not sufficient.**

Continuation of: Box V

There is nothing inventive in preparing dosage units of a pharmaceutically active compound, once the composition is known, and therefore claims 32 – 40, 60 - 61 lack inventive step. The applicant has not shown that there were any difficulties in preparing dosage units of compounds which have been shown in D2 to be pharmaceutically active. It may be that formulating a dosage unit may be complex, but the applicant has not shown this to be the case. D2 discloses that the compounds are useful as antioxidants in the mitochondria, and therefore the methods of claims 77 – 80 and 108 – 110 lack novelty and inventive step. While D2 does not specifically suggest that the compounds could be used to treat a patient, it would be obvious in view of the results presented by D2, that it could be used to treat a patient. Therefore the method of treatment of claims 91 – 95 lack an inventive step. D2 does not suggest that the compounds could be used to treat the conditions specified in claims 116 – 119, and therefore these appear to be novel and inventive.

D3 discloses that MitoQ, being a compound that falls within the scope of claims 1 – 10 and 53 – 57, is useful in preventing the cell death of fibroblasts from Friedreich Ataxia patients, and shows that such an effect is brought about by the antioxidant activity observed in mitochondria. This confirms their potential in treating Friedreich Ataxia. (see Abstract and Discussion) Therefore the compounds of claims 1 – 10 and 53 – 57 lack novelty and inventive step in view of D3. Knowing the compounds and their potential to treat Friedreich Ataxia means that preparing pharmaceutical compositions of the same compound is not inventive. Therefore the compositions of claims 11 – 19, 114 and 115, and dosage units of claims 32 – 40, 60 – 64 lack an inventive step. D3 does not suggest that the compounds could be complexed with cyclodextrin, and therefore claims 20 – 31, 65 - 76 comprising the complexes of MitoQ compounds and cyclodextrin may be novel and inventive, as are the corresponding dosage units of claims 41 – 52, and methods of use as claimed in claims 81 – 90 and 96 - 107. D3 discloses that oxidative stress in cells is reduced using compounds falling in the scope of the invention, and therefore the methods of reducing oxidative stress as claimed in claims 77 – 80, 108 – 110 lack novelty and inventive step, as are the methods of therapy as claimed in claims 91 - 95. The methods of treating Friedreich Ataxia of claims 116 – 119 lack novelty and inventive step in view of D3. D3 does not suggest a method of synthesis, and therefore claims 111 – 113 may be novel and inventive.

D4 discloses that MitoQ, being a compound that falls within the scope of claims 1 – 10 and 53 – 57, is an effective antioxidant when located in the mitochondria. This is ascertained in part by administering the compositions of mammalian cell cultures. D4 also discloses the synthesis of Mito-Q. Therefore the compounds of claims 1 – 10 and 53 – 57 lack novelty and inventive step. The pharmaceutical compositions of claims 11 – 19, 62 – 64, 114 and 115 lack inventive step, because the preparation of such compositions, in the face of the pharmaceutical benefits of Mito-Q compound revealed in D4, would be obvious. D4 does not suggest that the compounds are complexed with cyclodextrin, and therefore it is suggested that the pharmaceutical compositions of claims 20 – 31 and 65 - 76, and the dosage units of claims 41 – 52, and the methods of treatment of claims 81 – 90 and 96 – 107, may be novel and inventive. There is nothing inventive in preparing dosage units of a pharmaceutically active compound, once the composition is known, and therefore claims 32 – 40, 60 - 61 lack inventive step. D4 discloses that the compounds are useful as antioxidants in the mitochondria, and therefore the methods of claims 77 – 80 and 108 – 110 lack novelty and inventive step. While D4 does not specifically suggest that the compounds could be used to treat a patient, it would be obvious in view of the results presented by D4, that it could be used to treat a patient. Therefore the method of treatment of claims 91 – 95 lack an inventive step. D4 does not suggest that the compounds could be used to treat the conditions specified in claims 116 – 119, and therefore these appear to be novel and inventive. D4 does not reveal a method of synthesis which involves cyclodextrin, and therefore claims 111-113 may be novel and inventive.

(continued in Supplemental Box)

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

D5 discloses the synthesis of certain mitochondrially targeted anti-oxidant compounds, known as mitoquinol and mitoquinone, which fall with in the scope of claims 1 – 10 and 53 – 57. This then compromises the novelty and inventiveness of these claims. D5 also discloses the preparation of pharmaceutical compositions comprising these compounds, and this compromises the novelty and inventiveness of claims 11 – 19, 30, 31, 62 – 64, 114 and 115 as well as the dosage units of claims 32 – 40, 60, 61. (see D5 claims 15 – 22). D5 discloses that the antioxidant properties of mitoquinol and mitoquinone may be useful in treating certain disease including Parkinson's disease. Therefore the methods of claims 77 – 80, 91 – 95, 108 – 110, 116 - 119 lack novelty and inventive step.

D6 discloses that MitoQ, being a compound that falls within the scope of claims 1 – 10 and 53 – 57, is an effective antioxidant when located in the mitochondria, and that this elongates lifespan of fibroblasts. This is ascertained in part by administering the compositions of mammalian cell cultures. Therefore the compounds of claims 1 – 10 and 53 – 57 lack novelty and inventive step. The pharmaceutical compositions of claims 11 – 19, 62 – 64, 114 and 115 lack inventive step, because the preparation of such compositions, in the face of the pharmaceutical benefits of Mito-Q compound revealed in D6, would be obvious. D6 does not suggest that the compounds are complexed with cyclodextrin, and therefore it is suggested that the pharmaceutical compositions of claims 20 – 31 and 65 - 76, and the dosage units of claims 41 – 52, and the methods of treatment of claims 81 – 90 and 96 – 107, may be novel and inventive. There is nothing inventive in preparing dosage units of a pharmaceutically active compound, once the composition is known, and therefore claims 32 – 40, 60 - 61 lack inventive step. D6 discloses that the compounds are useful as antioxidants in the mitochondria, and therefore the methods of claims 77 – 80 and 108 – 110 lack novelty and inventive step. While D6 does not specifically suggest that the compounds could be used to treat a patient, it would be obvious in view of the results presented by D6, that it could be used to treat a patient. Therefore the method of treatment of claims 91 – 95 lack an inventive step. D6 does not suggest that the compounds could be used to treat the conditions specified in claims 116 – 119, and therefore these appear to be novel and inventive. D6 does not reveal a method of synthesis which involves cyclodextrin, and therefore claims 111-113 may be novel and inventive.

If the applicant was to fully and clearly describe, and claim the compounds of the invention and their uses and preparation in explicit terms, rather than merely in terms of the required result, then this may go a long way in overcoming the issues of novelty and inventiveness, and the observations.